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Perspective article

The thalamus integrates the macrosystems of the brain to facilitate complex, adaptive brain network dynamics

James M. Shine

Sydney Medical School, The University of Sydney, Australia

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ABSTRACT

The human brain is a complex, adaptive system comprised of billions of cells with trillions of connections. The interactions between the elements of the system oppose this seemingly limitless capacity by constraining the system's dynamic repertoire, enforcing distributed neural states that balance integration and differentiation. How this trade-off is mediated by the brain, and how the emergent, distributed neural patterns give rise to cognition and awareness, remains poorly understood. Here, I argue that the thalamus is well-placed to arbitrate the interactions between distributed neural assemblies in the cerebral cortex. Different classes of thalamocortical connections are hypothesized to promote either feed-forward or feedback processing modes in the cerebral cortex. This activity can be conceptualized as emerging dynamically from an evolving attractor landscape, with the relative engagement of distinct distributed circuits providing differing constraints over the manner in which brain state trajectories change over time. In addition, inputs to the distinct thalamic populations from the cerebellum and basal ganglia, respectively, are proposed to differentially shape the attractor landscape, and hence, the temporal evolution of cortical assemblies. The coordinated engagement of these neural macrosystems is then shown to share key characteristics with prominent models of cognition, attention and conscious awareness. In this way, the crucial role of the thalamus in mediating the distributed, multi-scale network organization of the central nervous system can be related to higher brain function.

The coordinated activity of a diverse population of specialized cells in the central nervous system forms the basis of our cognition, attention and conscious experience. Using the same set of interconnected neurons, we are capable of a striking array of different capacities. Once we learn an adaptive response to a particular context, our behaviour can be quite rigid and automatic, only to rapidly and flexibly reconfigure once circumstances change. Our brains are also capable of selecting and augmenting particular aspects of ongoing neural activity, such that portions of the neural landscape take on distinct phenomenological characteristics that sets them apart from the constantly churning background activity of the brain. Precisely how these distributed patterns of coordinated neural activity arise from a relatively fixed structural connectome (Honey et al., 2007; Betzel et al., 2013) in order to mediate the emergent effects associated with higher brain function remains poorly understood.

One of the major challenges faced by this line of enquiry is the demand to identify processes that cross multiple spatial and temporal scales across which the brain is organized. At the microscopic level, the brain is comprised of billions of cells, each with precise spatiotemporal characteristics that constrain its repertoire of functional interactions. At the macroscopic level, distributed patterns of coordination and competition amongst the cellular elements somehow give rise to emergent, collective behaviour observed in whole brain imaging studies. Recent advances in computational modelling (Breakspear, 2017) and deep learning (Richards et al., 2019) have made promising headway into these problems. Despite the many and varied benefits of these vantage points, they both clearly examine the function of the brain by interrogating the problem in the abstract. Therefore, to understand the manner in which the brain is able to instantiate complex, adaptive dynamics that span multiple spatial and temporal scales requires a closer interrogation of the precise manner in which the mammalian brain has solved the problem of organization across multiple spatial and temporal scales.

Another obstacle facing the field is that many of the leading theories for brain function in neuroscience have also mapped the functional capacities of the whole brain to the structure of the cerebral cortex. Given the striking anatomical prominence, recent phylogenetic expansion (Cisek, 2019; García-Moreno and Molnár, 2020) and the neurological sequalae of damage to its structure, it is perhaps unsurprising that the cerebral cortex has been the focus of theoretical explanations for cognition (Rao and Ballard, 1999), attention (Posner and Gilbert, 1999) and conscious awareness (Lau and Rosenthal, 2011). Indeed, at first glance, there is a compelling match between the computational capacity of the cerebral cortex and kinds of emergent behaviour we seek to explain (Bastos et al., 2012). It is also, at least in humans, the easiest

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structure to image with modern technologies, such that hypotheses targeted at the cortical level are easier to arbitrate between than their subcortically focused counterparts. However, closer examination of the microstructural connections of the cerebral cortex reveals crucial interconnections with a number of subcortical structures, including the thalamus, the tectum, the basal ganglia and the cerebellum. Each of these subcortical structures receives precise input from, and projects precisely back to, specific and unique compartments of the cerebral cortex. This suggests that the interactions between the cerebral cortex and the subcortex likely place important constraints on the manner in which the cerebral cortex can function, which in turn, will shape the dynamic processes that form the basis of our conscious experience. Indeed, there is now compelling evidence that many of these crucial capacities depend more directly on subcortical structures than activity within the cerebral cortex (Hong et al., 2018; Takahashi et al., 2020).

A potential solution to these two challenges involves investigating the mesoscopic connections between different well-defined microcircuits, such as those that are known to comprise the cerebral cortex (Douglas and Martin, 1994), the thalamus (Jones, 2001), the basal ganglia (Wilson, 2013) and the cerebellum (Montgomery and Perks, 2019). Recent technological advances now afford researchers access to detailed maps of these circuits, which have helped to clarify the precise manner in which the different sub-systems interact structurally (Harris et al., 2019; Phillips et al., 2019). However mere knowledge of the structural connections between regions is an insufficient means for inferring the functional capacities of the brain, which emerge from coordinated interactions between elements distributed around the central nervous system, the body and the environment (Grillner, 2003). One way to make progress in this area is to create computational models of neural architecture, in an effort to better understand the principles that characterize the organization of the brain (Breakspear, 2017). Another promising strategy is to interrogate the emergence of different brain regions or circuits over phylogeny, in an effort to link structural innovation with functional adaptation (Cisek, 2019). Both approaches have led to crucial insights into the biological mechanisms that instantiate our behaviour.

A complementary strategy involves synthesizing results from across the literature to provide a theoretical account of how the interactions between different specialized circuits within the brain work together in order to facilitate functional, adaptive behaviours. This approach has the potential to link advances in empirical neuroscience with the lessons learned from more theoretical, computational modelling studies. In this Perspective, I use this approach to demonstrate an organizing principle across the central nervous system that rests on the mesoscopic coordination between the well-defined microcircuits of the cerebral cortex, thalamus, basal ganglia and cerebellum. Specifically, I focus on previous work that has demonstrated that distinct layers within the cerebral cortex receive input from unique thalamic populations (Clascá et al., 2012; Jones, 2001; Phillips et al., 2019), which in turn shape the processing mode of the cerebral cortex. These same thalamic populations also receive broadly segregated inputs from the cerebellum or basal ganglia (Kuramoto et al., 2009). I argue that it is these subcortical inputs that provide the basis for the unique processing modes within the cerebral cortex that form the basis of a parallel, content-based, circuitry and a serial, context-based circuitry, respectively (Jones, 2009; Llinás and Ribary, 2001).

To effectively characterize these different dynamic modes of organization, I leverage the language of dynamical systems theory, which conceptualizes systems-level activity in the brain as a set of spatiotemporal trajectories that evolve across an attractor landscape (Bressler and Kelso, 2016; Pessoa, 2019). The distinct circuit properties of the cerebral cortex, thalamus, basal ganglia and cerebellum, along with the connections between the different structures, are proposed to shape and constrain the manner in which these spatiotemporal trajectories evolve over time. Specifically, cerebellar-mediated, core thalamic inputs are proposed to facilitate relatively segregated, feed-forward modes that allow for parallel attractor landscape trajectories, whereas basal ganglia-mediated, matrix thalamic inputs are instead proposed to force the system into an integrative, feed-back modes that enforce serial trajectories onto the attractor landscape. Local interactions between these two systems are then further proposed to shape the spatiotemporal trajectories of nervous system dynamics in order to maximize adaptive fitness. Together, the interactions between distributed neural microcircuits are argued to together form the basis of the systems-level brain dynamics that instantiate processes involved in both action specification and selection.

The manuscript is organized into three separate sections: the first details known anatomical relationships between the thalamus, cerebral cortex, basal ganglia and cerebellum; the second section then describes the manner in which these different principles of connectivity theoretically relate to the evolution of spatiotemporal trajectories across an attractor landscape; and in the final section, an attempt is made to link these dynamical organizing principles to emergent properties of whole brain function, such as learning, cognitive function and cognitive awareness. Throughout this investigation, it becomes clear that the thalamus plays a crucial role in the mediation of the distributed network organization of the central nervous system that forms the basis of higher brain function.

1. Distinct thalamocortical systems uniquely shape cortical activity modes

Located at the intersection between the hypothalamus, telencephalon and brainstem, the thalamus is ideally placed to impact whole-brain functional modes (Halassa and Kastner, 2017; Halassa and Sherman, 2019; Jones, 2009, 2001; Poulet et al., 2012; Sherman, 2007). A relatively small, bilateral structure in the diencephalon, the thalamus receives diverse connections from across the central nervous system and sends axonal projections to the entire cortical mantle and striatum. Activity patterns within the thalamus are fundamentally different during sleep and wake cycles: the major relay nuclei fire in bursts during sleep, but tonically while awake (Steriade et al., 1993). Despite their persistent spiking activity during periods of high arousal, the thalamic nuclei are considerably damped by activity-dependent spiking activity in the GABAergic reticular nucleus (Halassa and Acsády, 2016; Steriade et al., 1986). Thus, the thalamus is able to balance excitatory inputs with local inhibition in order to shape the information processing mode of the rest of the brain, particularly the cortex (Halassa and Sherman, 2019) and striatum (Smith et al., 2004).

At the microscopic level, the thalamus is comprised of an admixture of different classes of excitatory neurons that project in strikingly different ways to the cerebral cortex (Clascá et al., 2012; Jones, 2001; Rubio-Garrido et al., 2009). Parvalbumin-staining core cells (Fig. 1A; blue) act as drivers of activity by sending projections to layers III and IV of the cerebral cortex, whereas calbindin-staining matrix cells (which are more common in higher-order thalamic nuclei; Herkenham, 1979; Honjoh et al., 2018; Jones, 2001) preferentially target agranular cortices. Individual thalamic nuclei contain a blend of both cell-types (Fig. 1A), and there is recent evidence that some thalamic cells contain elements of both types of connections (Clascá et al., 2012), suggesting that it is perhaps best to conceptualize thalamic neurons as existing along a spectrum. Interestingly, these different thalamic populations also receive distinct patterns of excitatory input from the cerebral cortex (Sherman and Guillery, 2002; Bickford, 2016), suggesting that they may also process unique modes of cortical information.

The cortical regions receiving predominantly core input are often those that are relatively tethered to input from sensory channels (Buckner and Krienen, 2013), such as the retina and cochlea (Jones, 2001). These cortical regions typically contain a prominent granular layer IV and stain heavily for parvalbumin interneurons (Kepecs and Fishell, 2014). According to the canonical microcircuit model of the cerebral cortex, input from the core thalamic nuclei to the stellate cells

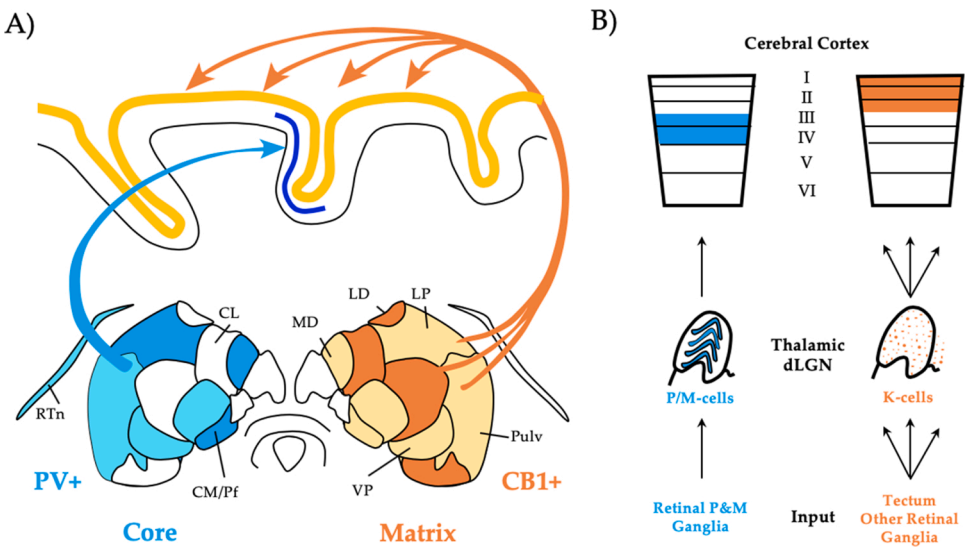

Fig. 1. Two ends of a thalamocortical connectivity spectrum. A) A simplified circuit diagram of the matrix (orange) and core (blue) thalamocortical architectures. Inputs from the parvalbumin-rich (PV+) core cells preferentially target granular layers of the cerebral cortex, whereas calbindin-rich (CB+) matrix thalamus preferentially target the supragranular layers of the cerebral cortex; B) the dorsal lateral geniculate nucleus of the thalamus (dLGN) offers a paradigmatic example of the different information processed by the two circuits: parvo- and magno-cellular cells in the retina (P and M, respectively) send colour and motion signals to the PV+ core cells, whereas more diffuse signals from the retina and tectum are transmitted to the CB+ koniocellular (k-cells). Figures adapted from Jones (2001).

of the cerebral cortex sends driving activity (Douglas and Martin, 2004) to the intra-telencephalic (IT-type) pyramidal cells in the same column that promote feed-forward activity (Gal et al., 2017; Markov et al., 2014). The IT-type cells also increase the multiplicative gain of layer V pyramidal tract (PT) type pyramidal cells that send outputs to the subcortex (Pluta et al., 2015). The input to layer IV stellate cells also makes contact with the same layer VI cortico-thalamic (CT) type pyramidal neurons that selectively project back down to both the core nucleus that innervated the same region (Jones, 2001). Together, this can amplify signal gain through processes that resemble divisive contrast normalization (Crandall et al., 2015; Lien and Scanziani, 2013), however only at particular frequencies (e.g., ~10 Hz; Fogerson and Hugengard, 2016; Kirchgessner et al., 2020). This positive feedback loop would rapidly spiral out of control and fire at high frequencies, were it not for the potent inhibitory impact of the GABAergic reticular nucleus (Steriade et al., 1986). To ensure this dampening behaviour, the layer VI corticothalamic pyramidal cells innervate the reticular nucleus on the way to the major excitatory cells of the thalamus. This has the effect of either boosting or silencing activity within the thalamocortical loop, depending on the frequency and timing of the circuit's engagement (Crandall et al., 2015; MacLean et al., 2005; Saleem et al., 2017).

In contrast to the relatively selective projections of core thalamic cells, calbindin-staining matrix cells are thought to fulfil a more modulatory function (Cruikshank et al., 2012; García-Cabezas et al., 2019; Jones, 2009, 2001). They do so by contacting infra- and supra-granular regions of the cerebral cortex in a much more diffuse pattern than the core nuclei (Jones, 2001; Fig. 1A). In contrast to core cells, matrix thalamic cells receive more diffuse, and less spatially precise input, typically from the tectum and koniocellular retinal ganglia (Jones, 2001; Fig. 1A). In turn, the matrix cells also project more diffusely to the supragranular layers of cortex, often spreading across multiple neural regions (Jones, 2001; Fig. 1B). It is in the supragranular layers of the cerebral cortex that the matrix thalamic cells make contact with the apical dendrites of IT-type and PT -type pyramidal cells (Harris and Shepherd, 2015; Rubio-Garrido et al., 2009; Solari and Stoner, 2011) that are also the primary site of relatively diffuse 'feedback' connections from more higher (i.e., more agranular) cortical regions (Douglas and Martin, 2004; Fig. 1A). Here, the matrix cells non-linearly modulate the gain of the pyramidal cells (Roth et al., 2016) and thus help to integrate feedback from higher (i.e., more agranular) regions and promote an integrative functional mode that may form the basis of a distributed context signal that binds the relatively specific core cells into a distributed coalition (Varela et al., 2001). Importantly, there is also evidence that matrix thalamic cells contact inhibitory late-spiking, neurogliaform interneurons in the supragranular regions of cortex (Cruikshank et al., 2012), suggesting that they may also act to constrain activity to their targeted neurons by inhibiting layer III pyramidal cells that would otherwise propagate activity to higher regions of the cerebral cortex. These synaptic connections are also important sites of learning-induced plasticity in the cortex (Williams and Holtmaat, 2019). Together with evidence demonstrating that the thalamostriatal connections that arise from these matrix thalamic populations are also crucial for learning (Logiaco et al., 2020; Murray and Escola, 2020), these findings suggest an important role for thalamocortical matrix connections in shaping relatively automatic behaviours. Together, these lines of evidence extend and refine the hypothesis that the core thalamic cells promote feedforward processing, whereas the matrix thalamic cells promote contextual, feedback processing (Jones, 2009).

2. Distinct thalamic populations receive different inputs from the subcortex

With an appreciation of the main processing modes present within the thalamocortical system, the different inputs to the thalamus become of crucial importance for understanding how the state of the cerebral cortex will iteratively change over time. The nuclei of the ventral tier of the thalamus (the ventral anterior, ventral lateral and mediodorsal nuclei) are of particular importance for defining the dynamics of frontal cortical regions, which in turn provide constraints over much of the rest of the central nervous system. Crucially, the core and matrix thalamic subpopulations receive strikingly different driver inputs from different subcortical systems (Fig. 2): parvalbumin-staining core cells predominantly receive glutamatergic inputs, either from sensory nuclei (Jones, 2001), from association cortical regions (Sherman, 2007), or from the deep cerebellar nuclei of the cerebellum (Kuramoto et al., 2009), whereas calbindin-staining matrix cells are instead under the GABAergic control of the globus pallidus internus, which is the final inhibitory pathway from the basal ganglia (Kuramoto et al., 2009). This suggests that distinct channels of either raw or processed neural information are transmitted back to the cerebral cortex via distinct populations of thalamic cells (Fig. 2), where they then shape and constrain the evolving dynamics across the cortical mantle.

The cerebellum also provides glutamatergic input to the ventral tier of the thalamus (Fig. 2). Across the cortical mantle, PT-type layer V pyramidal cells in the cerebral cortex send projections to the pontine nuclei in the brainstem, wherein they innervate a massive population of cerebellar granule cells (Montgomery and Perks, 2019). Granule cell axons form the parallel fibres of the cerebellar cortex where they make

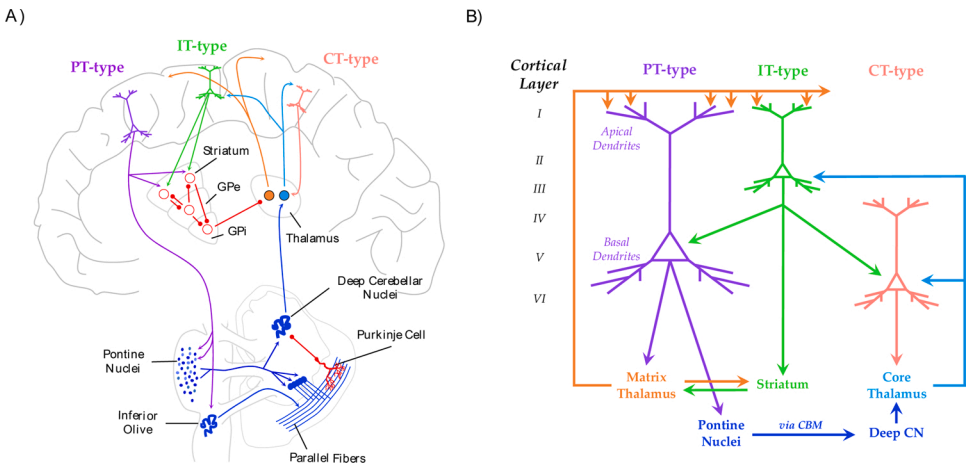

Fig. 2. The effect of basal ganglia and cerebellar input on core/matrix attractor dynamics. A) Each thalamic population within the ventral tier typically receives distinct inputs from basal ganglia (GABAergic input to matrix thalamus) or cerebellum (glutamatergic input to core thalamus); B) simplified circuit diagram of connections between the three major classes of excitatory cortical pyramidal cells (connections between regions not shown). Key – pyramidal-tract (PT) type (purple); intra-telencephalic (IT) type (green); cortico-thalamic (CT) type (salmon); GABAergic inhibitory cells (green); cerebellar (blue); core thalamus (light blue); matrix thalamus (orange); GPe – globus pallidus externus; GPi – globus pallidus internus.

diverse contacts with the dendrites of Purkinje cells, which in turn actively shape the activity of the deep cerebellar nuclei by precisely releasing specific subsets of the nuclei from tonic inhibition (Person and Raman, 2011). These nuclei, which are the only output structure of the cerebellum, make contact the core nuclei of the ventral thalamus, along with the magnocellular red nucleus (Donkelaar, 1988). The flow-on effect of this disinhibition is to increase the gain of parvalbumin-enriched core thalamic nuclei (Houk and Wise, 1995; Kuramoto et al., 2009), and hence to drive the cerebral cortex in a feedforward mode of processing. In such a manner, the cerebellum is able to translate an efference copy of layer V PT-type cortical pyramidal cell activity into a rapid anticipation of the sensory consequences of motor actions (Blakemore et al., 2001). This process acts as a *"comparator of intentionality with execution"* (D'Angelo and Casali, 2013), while also acting as an adaptive filter that effectively cancels out self-generated noise (Montgomery and Perks, 2019). Importantly, the diversity of the granular cell population (Montgomery and Perks, 2019) and the projections of deep cerebellar nuclei to the core nuclei of the ventral thalamic tier also allow for the cerebellum map novel stimuli to highly adaptive pre-existing responses (Koziol et al., 2012).

The basal ganglia also innervate the ventral tier of the thalamus via an multi-synaptic inhibitory circuit that respects the rostro-caudal gradient of connectivity present in the cortex (Fig. 2; Dunovan et al., 2015). Under glutamatergic drive to otherwise quiescent striatal projection neurons, GABAergic spiny neurons of the striatum inhibit otherwise tonically active GABAergic pallidal neurons, particularly when levels of tonic dopaminergic input are elevated. This has the effect of releasing patterns of ongoing activity in brainstem nuclei that often descend further down to the spinal cord to control movements (Takakusaki, 2013) or autonomic functions (Cho et al., 2013). In addition to these brainstem afferents, the globus pallidus also projects to the ventral tier of the thalamus. Originally, it was presumed that these GABAergic neurons contacted core thalamic cells, and thus released a cortical circuit to promote a particular action plan (e.g., in motor cortex) (Alexander, 1986). However, closer anatomical scrutiny reveals that pallidal neurons actually make preferential contact with calbindin-staining thalamic matrix cells (Kawaguchi, 2017; Kuramoto et al., 2009), which in turn project more diffusely to supragranular regions of cortex (Clascá et al., 2012). Thus, striatal activity would have the effect of releasing a matrix cell from pallidal inhibition, which in turn would augment activity within a small patch of supragranular activity (Rubio-Garrido et al., 2009; Fig. 2B). The diffuse nature of many of these connections implies that the traditional notion of a corticostriatal loop (Alexander, 1986) is perhaps more tenuous than previously appreciated.

If the striatum doesn't act to release a specific corticothalamic loop, then what is its effect on cortical activity? Pallidal GABAergic inputs predominantly contact matrix thalamic cells (Kuramoto et al., 2015), which send diffuse projects to the supragranular layers of the cerebral cortex (Clascá et al., 2012). In other words, the projections of the thalamic cell that is disinhibited by the globus pallidus would send excitatory projections to the supragranular layers of a number of excitatory cells, not just the cell that recruited the striatal-mediated disinhibition of the thalamic matrix cell. The basal ganglia would initiate a feed-forward loop of neuronal firing that was constrained to the local cortical architecture, but in a manner that is distributed to the local neuronal population in the cortex (rather than just the cell that triggered the initial response). Importantly, this enhancement would be limited to the set of columns that were otherwise relatively active based on the current behavioural context (i.e., those PT-type cells that sent an efference copy in the cells recent history). Rather than the traditional notion of the release of an action plan (Goldberg et al., 2013; Graybiel, 2008), this process would instead mediate a relatively localized search of the local cortical architecture, with the constraints imposed by the specific connections of the currently active pyramidal cells. There is recent evidence from a study investigating both humans and monkeys that directly supports these hypotheses (Wang et al., 2020).

Studies of basal ganglia circuitry during birdsong (Charlesworth et al., 2012; Kojima et al., 2018; Woolley et al., 2014) also support this process, and further suggest that the basal ganglia likely plays distinct roles in different stages of learning. Early in the course of learning, the basal ganglia are crucial for learning novel stimuli in the course of skill acquisition (perhaps by augmenting constrained variability), but later in the course of learning (i.e., once skills have become otherwise fully automatized), the same structures are more important for mediating exploratory variability. By releasing matrix cells from tonic inhibition, the basal ganglia can essentially imbue the cortex with an increase in neural variability. From this mechanism, it is possible to hypothesize a direct link between neuronal variability and the behavioural variability known to be required for effective motor learning (Bell, 2017; Charlesworth et al., 2012; Honegger and de Bivort, 2018) or cognitive task performance (Garrett et al., 2011; Wu et al., 2014), however this prediction requires further empirical confirmation.

The synaptic targets of the basal ganglia and cerebellum are known to be segregated at the level of the thalamus, suggesting that the two subcortical systems imbue the brain with different functional capacities. Despite this anatomical separation, recent work has argued that there are a number of di-synaptic connections that interconnect the two structures (Bostan and Strick, 2018; Bostan et al., 2010). For instance, the subthalamic nucleus, a major glutamatergic structure within the basal ganglia, has been shown to make excitatory contacts with the pontine nuclei, which in turn innervate the massive population of granule cells in the cerebellum. In addition, while the majority of thalamic connections from the deep cerebellar nuclei contact core thalamic cells (e.g., in the ventral lateral and mediodorsal nuclei;

Kuramoto et al., 2009; Prevosto and Sommer, 2013), there are known connections between the cerebellum and the intralaminar nuclei of the thalamus (specifically, the central lateral nucleus; Habas et al., 2019; Milardi et al., 2019), which in turn heavily innervate the striatum. In addition, the two structures could in principle communicate through an intermediary in the cerebral cortex, though current evidence suggests that distinct classes of pyramidal cells innervate the pontine nuclei and striatum (PT-type and IT-type, respectively; Economo et al., 2018; Takahashi et al., 2020). For these reasons, it is important that future work clarifies the implications of these different subcortical interactions for shaping whole brain functional modes.

The evidence reviewed above provides a neurobiological process by which distinct populations of thalamic nuclei can utilize the unique computational benefits inherent within separate sub-cortical systems to shape and constrain the processing mode of the cerebral cortex. But how does this system instantiate the dynamics required to mediate flexible, integrative and specific processing characteristic of adaptive behaviour? In the next section, I argue that, through their contrasting projections to the cerebral cortex and distinct subcortical inputs, the core and matrix populations of the ventral thalamus differentially impact the manner in which ongoing cortical state dynamics evolve over time.

2.1. Thalamocortical constraints over attractor landscape dynamics

Through strong connections with the subcortex, the cerebral cortex greatly benefits from the computational capacities inherent within the thalamic, basal ganglia and cerebellar circuitries (Houk and Wise, 1995). Together, these interactions form the basis of a complex, adaptive system, distributed across the central nervous system (Cisek, 2012). The interactive nature of these circuits, each with their own characteristic spatiotemporal constraints, suggests that the combined activity of the brain will likely follow the logic of circular causality (Bizzarri et al., 2019; Juarrero, 2002). Somewhat counter-intuitively, in systems with circular causality, the activity at the microscopic level both defines the activity macroscopic scale and is constrained by this same activity. The emergent signatures from a dynamical system organized in this fashion are also often highly non-linear (McIntosh and Jirsa, 2019). Together, these considerations suggest that viewing the cerebral cortex in isolation (i.e., without an appreciation of its interaction with the thalamus, basal ganglia and cerebellum) has the potential to lead to an overemphasis of its importance and also to erroneous claims of its isolated role in the functional capacities of an organism.

Fortunately, there is a useful vantage point from which these circular

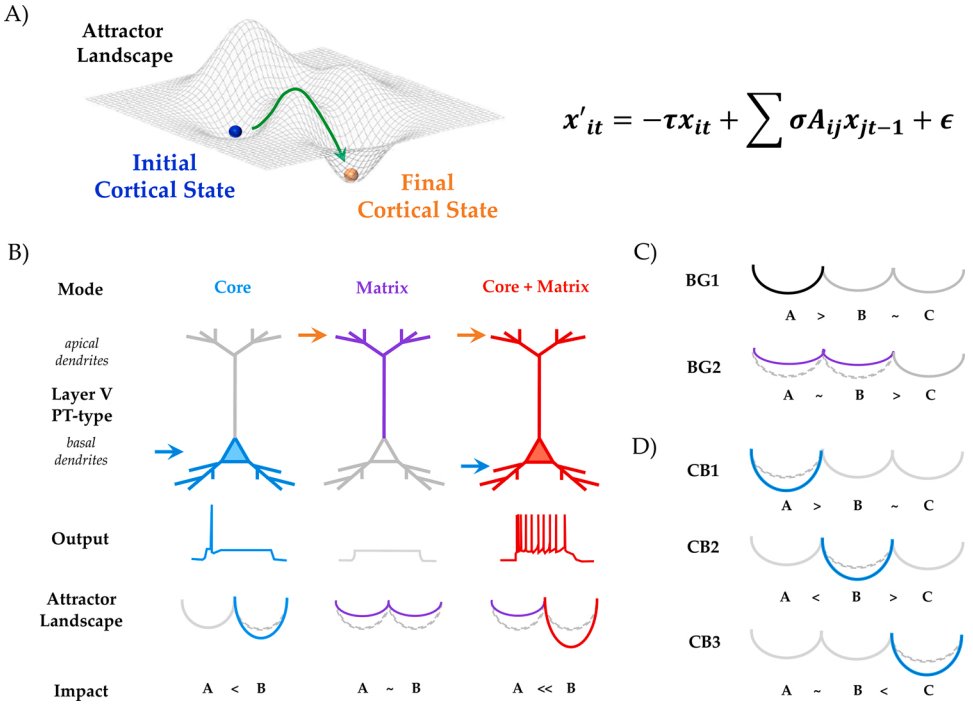

Fig. 3. Distributed activity in the central nervous system defines a trajectory across an attractor landscape. A) Graphical depiction of an attractor landscape, where the distributed brain state across the cortex ('x') is defined as a point in state-space, and the connectivity between regions (A_{ij}) defines the topography of the landscape – the topography relates directly to the dynamical systems equation (Breakspear, 2017) that defines the brain states trajectory over time: the change in x (x') over time is related to a weighted value of its own previous activity (τ), plus the activity from connected regions, weighted by a gain function (σ) and some added noise (ε); B) Layer V PT-type pyramidal cells have a unique topography, with basal dendrites, which are close to the cell body and cause spiking activity, and apical dendrites, which sit in the supragranular layer and are electrically isolated from the cell body by HCN *Ih* channels. Feed-forward (light blue) and feedback (orange/purple) inputs of operation are insufficient to cause the pyramidal cell to burst – this only occurs when the two patterns coincide within a temporal window (red21,74). Similar to the way in which a ball would roll down a hill under the force of gravity, state-based neural dynamics can be conceptualized as the flow of the system on a dynamically evolving attractor landscape, in which the *x* coordinates represent hypothetical brain states and the peaks and valleys (i.e., the *y* coordinates) represent the 'energy' needed to reach each state (note: the real brain state would of course be embedded in far more than one dimension (McIntosh and Jirsa, 2019)); C) Proposed effect of basal ganglia involvement on attractor landscape topology: activation of column *A* (BG1) leads to recruitment of matrix that cells that flatten the energy barrier separating *A* and *B*, but not *C* (BG2) – see the main text for further details; D) Proposed effect of cerebellar involvement on attractor landscape topology: activation of column *A* (CB1) is associated with the cerebellar-mediated recruitment of *B* (CB2), which is then followed rapidly by *C* (CB3) – see the main text for further details.

dynamics can be properly appreciated. Specifically, the distributed pattern of neural dynamics that arises from the corticothalamic system can be conceptualized as the flow of the system on a dynamically evolving attractor landscape (Fig. 3), in which the peaks and valleys represent a topography across which the brain state travels (following something similar to a law of gravity). The basic intuition is straightforward: reaching peaks requires an influx of energy, whereas it is somewhat trivial to roll with gravity down into a valley. In this framework, the evolution of the distributed state of neural activity over time (e.g., during the course of learning) represents a specific trajectory across the attractor landscape (Spivey and Dale, 2006). Importantly, the attractor landscape is not a mere analogy, as the evolution of the brain state over time (i.e., a ball rolling across the landscape) maps directly to the equations that govern the generation of neural activity (Fig. 3A). In analogy to the manner in which the products of individual genes interact with one another to form a phenotypic landscape, the topography of the brains' attractor landscape is shaped by the patterns of activity of individual cortical regions, but it is their combined activity that is most important for defining the flow of activity over time (Fig. 3A).

Within the attractor landscape framework, dynamics can be conceptualized as being driven by a set of attractors, which are idealized brain states that the system evolves towards, despite starting from a wide variety of initial conditions (Miller, 2016). Knowledge of a nodes attractors is therefore an important determinant in defining how distributed activity across the brain will evolve over time in order to mediate complex, adaptive behaviours. Importantly, attractors can exist at multiple different spatiotemporal levels in the brain, including the cellular, circuit and systems levels. However, much in the way that the algorithmic functions of an airplane are best described at the level of functional parts, rather than the atomic level (Pessoa, 2019), in the Perspective detailed here, the crucial level of explanation for attractor dynamics is proposed to exist, not at the level of the individual neuron, but at the circuit level. Specifically, the engagement of distinct cortico-subcortico-thalamo-cortical circuit motifs is hypothesized to mediate the formation (and dissolution) of quasi-stable, fixed-point attractors (Müller et al., 2020b), that in turn shape the systems-level evolution of brain state dynamics.

A key prediction of this work is that distinct modes of processing within the thalamocortical system should act to shape spatiotemporal attractor dynamics, and hence, alter the spatiotemporal evolution of the brain over time. These thalamocortical attractors can be conceptualized as valleys that emerge dynamically and act to pull the evolving brain state towards them (i.e., as if pulled by gravity). In contrast, peaks in the attractor landscape are proposed reflect a relative increase in local inhibition (likely mediated by a relative increase in GABAergic reticular nucleus activity). Consistent with the intuition of climbing a hill, these peaks would require a substantial influx of energy (i.e., neural activity) to be reached. Importantly, the attractors in this framework are proposed to be relatively transient (Rabinovich et al., 2008), and hence to together form a kind of 'winnerless competition' with one another in order to drive ongoing whole-brain dynamics.

In contrast to the three-dimensional world in which we live (and where many of our intuitions for these concepts are built), the attractor landscape that defines human brain state dynamics will undoubtedly have an extremely large dimensionality. Using estimates from human anatomical studies (Herculano-Houzel, 2009), and the knowledge that ~80 % of cortical cells are excitatory pyramidal cells (Buszáki et al., 2007), there are roughly ~20 billion excitatory pyramidal cells in the cerebral cortex of an adult human. Assuming that each cell can exist in one of two activity states (i.e., spiking or quiescent, which is itself likely an over-simplification), then these excitatory cells can instantiate a staggering $\sim 2 \times 10^{20}$ different unique states – a veritable combinatorial explosion. While this number might be taken as an approximate upper bound for the dimensionality of the landscape, in practice the dimensionality of this space is likely constrained by the lower-dimensional architectures of the striatum (Bar-Gad et al., 2003), thalamus (Shine et al., 2019b) and colliculus (Takahashi et al., 2020), as well as the known degeneracy present within the cerebral cortex (Tononi et al., 1999). The precise dimensionality of the attractor landscape is however not of major concern, as the basic intuitions developed at low-dimensions should essentially scale to higher-dimensions. With these challenges in mind, in the following section, I detail a number of predictions regarding the specific manner in which mesoscopic circuit dynamics might impact spatiotemporal brain state dynamics.

The engagement of the core circuitry is hypothesized to engage a rapid (but relatively short-lived) deepening of an attractor valley (Fig. 3B; left). Depending on the regions' connection to other currently active neural coalitions, the global brain state would likely incorporate this region into its expression, and the balls representing excitatory cortico-thalamic circuits would roll into the newly formed valley (i.e., as if enslaved by the new attractor). A column driven in this manner is hypothesized to run in relatively deterministic, feed-forward mode, and so long as the circuit's engagement leads to effective performance (e.g., through optimal coordination; Bressler and Kelso, 2016), is hypothesized to support parallel processing across the brain. Similar to the multi-ball mode on a pinball machine, a system running in this mode is analogous to multiple balls (or segregated groups of balls) rolling across the landscape, each defined by their own separate attractor. Importantly, this mode could only function appropriately under circumstances in which there is a well-learned interaction between the body and the world (for instance, after multiple years of driving the same car on a familiar route). Any mismatches between cerebellothalamocortical anticipatory predictions and the affordances mapped by the sensory system would otherwise lead to impaired performance, which in turn would force the system to evolve in a different manner (i.e., by utilizing feed-back processing modes, or alterations in the tone of the ascending arousal system).

In contrast to the core circuitry, if the matrix input into a set of distributed regions were increased, this would make it more likely that each of the cortical regions to which the matrix cell projected could potentially be included in an upcoming brain state. This is equivalent to flattening a small section of the attractor landscape (Fig. 3B; middle), and essentially creating a broader attractor basin for the brain state to evolve towards (Müller et al., 2020b). Therefore, matrix inputs facilitate variability that actually promote constancy (Bell, 2017; Honegger and de Bivort, 2018), while also injecting an element of randomness into the otherwise deterministic, feed-forward processing mode mediated by the core circuitry. This randomness need not be maladaptive and could instead represent a means for not becoming stuck in local minima on the attractor landscape (Müller et al., 2020a, 2020b). The diffuse nature of the matrix thalamic projections to the supragranular regions of the cerebral cortex, along with the fact that burst-firing in layer V PT-type pyramidal cells innervates both the matrix thalamus and superior colliculus (Takahashi et al., 2020), suggests that the cortical regions recruited into this mode of firing would become inextricably bound together into a single, evolving mode. Through this mechanism, I hypothesize that pyramidal cells that have transitioned into a burst-firing mode, and have not been actively segregated from the rest of the network (e.g., by inhibitory activity in the cerebral cortex or thalamus), will be recruited into the serial mode of processing that characterizes the more deliberate psychological processes (Robbins and Costa, 2017) that comprise conscious awareness (Rabinovich and Varona, 2017).

An important implication of this model is that the interactions between core and matrix thalamocortical circuits are a crucial factor that differentiates distinct information-processing modes in the cerebral cortex (i.e., parallel, automatic vs. serial, deliberate processes). There is existing empirical evidence to support this notion. Specifically, when action potentials that reach the basal and apical dendrites of PT-type pyramidal cells coincide within a precise (<30 msec) window (Larkum et al., 2009), there is evidence that the neurons undergo an 'apical amplification' and transition into a burst mode of firing (Fig. 3B; right), that strongly increases their signal-to-noise properties (Larkum et al.,

2009). This would be reflected in a rapid and sustained deepening of the attractor well (Fig. 3B; right), which would in turn make it more likely for the particular attractor to influence the evolving brain state. Hypothetically, the duration of the attractor well remaining sufficiently deep so as to enslave the ongoing brain state should be directly proportional to the burst firing rate of the pyramidal cell population, which could in turn be augmented by recurrent activity. Through this process, feed-forward (via layer III IT-type pyramidal cells) and feedback signals (via layer V PT-type pyramidal cells) interact so as to allow the matrix system to augment the otherwise automatic, core circuits that had been engaged within that temporal window, either via sensory (Kuramoto et al., 2009) or cortical (Sherman, 2007) input. In this way, locally activated circuits can be conceptualized as arising due to a relatively constrained (or directed) arousal state that is mediated by higher-order, matrix thalamocortical interactions (Nakajima and Halassa, 2017). A system organized in such a way could feasibly facilitate distributed decision making (Powers, 1973) by providing a dynamic platform for distinct circuits to run in both serial (Rabinovich and Varona, 2017) and parallel (Foote and Morrison, 1987), without the need for a centralized controller.

Within this context, the importance of distinct inputs to the thalamus from the basal ganglia and cerebellum, each with their own characteristic processes defined by unique internal circuitries, can now be appreciated. Under glutamatergic drive to otherwise quiescent striatal projection neurons, GABAergic spiny neurons of the striatum inhibit GABAergic pallidal neurons, which in turn 'release' patterns of ongoing activity in brainstem nuclei that often descend further down to the spinal cord to control movements (Takakusaki, 2013) or autonomic activity (Cho et al., 2013). In addition, similar pallidal disinhibition allows the recruitment of relatively diffuse matrix thalamic feedback to the supragranular cortex, which in turn augment dendrites within a patch of supragranular cortex (Rubio-Garrido et al., 2009). This would lead to a relative flattening of a specific portion of the attractor landscape (Fig. 3C), increasing variability in a way that is limited and constrained by the current behavioural context (i.e., the PT-type cells that fired to recruit the striatum) and the prior history of the organism (i.e., the synaptic weights connecting different neural populations according to previous experience). I propose that this process will imbue the brain state with a measure of indeterminancy, which has been suggested by others as a potential means for imbuing an organism with the capacity of volitional choice (i.e., 'free will'; Brembs, 2011; Mitchell, 2018). While this process is mechanistically distinct from the traditional notion basal ganglia function, in which the pallidum was presumed to 'release' an action plan (Goldberg et al., 2013), it does provide a potentially more parsimonious explanation for the known increase in variability that is required for both effective motor learning (Bell, 2017; Charlesworth et al., 2011; Honegger and de Bivort, 2018; Wang et al., 2020) and cognitive task performance (Garrett et al., 2011).

As mentioned above, the organization of the cerebellum is far more modular than the basal ganglia and cerebral cortex. Through this circuitry, the cerebellum is able to learn to minimize the difference between unconditioned stimuli and conditioned responses (Koziol et al., 2013). Over the course of learning, a distributed spatiotemporal Purkinje cell activity pattern releases a subset of the deep cerebellar nuclei from inhibition (Person and Raman, 2011). The flow-on effect of this disinhibition is to increase the gain of parvalbumin-enriched core thalamic nuclei (Houk and Wise, 1995; Kuramoto et al., 2009), which in turn enhance thalamocortical activity precisely within the cortical columns that are expected to occur next in the sequence of activity that was previously learned by the cerebellar cortex (Leiner and Leiner, 1997; Jirenhed et al., 2017). In this way, the cerebellar architecture can mediate the execution of the precise spatiotemporal sequence (e.g., $A \rightarrow B \rightarrow C$; Montgomery and Perks, 2019) through a systematic temporal modulation of the attractor landscape, without needing substantial input from the cortex (Fig. 3D). Viewed accordingly, the cerebral cortex and basal ganglia could act to start off a sequence (i.e., by transitioning a layer V PT-type pyramidal cell into burst firing mode; Tang and Nibley, 2019), and then use the efference copy of the bursting dynamics to trigger a well-learned, relatively automatic sequence of activity within the cerebellar cortex. This would have the effect of driving the core nuclei of the thalamus (and hence, their connected cortical regions) in a manner consistent with the execution of the previously learned sequence of behaviour (Thach and Jones, 1979), essentially freeing up the cerebral cortex for shaping and refining more high-dimensional aspects of the ongoing process. Therefore, the mesoscopic instantiation of habitual and automatic processing requires the coordinated interaction of many regions distributed across the central nervous system.

2.2. Alternative paths for predictive processing in the brain

The process described here suggests a potentially novel implementation of classical models of whole brain inference. While there is now overwhelming consensus that the brain acts as a predictive processing machine (Spratling, 2016) – that is, expectations based on prior experience constrain the set of possible stimuli that can be observed in the environment – there is less agreement regarding precisely how this capacity is instantiated in the brain (Spratling, 2017). In previous work that focussed predominantly on the cerebral cortex (Rao and Ballard, 1999), it has been suggested that predictions are sent from higher, agranular regions to lower, granular regions (Fig. 4; $Prior_{CTX}$). The predictions represent a set of prior expectations for the incoming input from the sensory system. The difference between the inputs that actually arrive and the prior expectations is then combined to form the basis of a prediction error signal, which is then proposed to propagate back up the hierarchy, potentially informing more agranular regions of the mismatch (Spratling, 2002).

As I have argued in this Perspective, it is important to take non-cortical connections into account when characterizing the functionality of the brain. In particular, the cerebellum is well-placed to play a crucial role in instantiating predictive processing within the central nervous system. Specifically, I hypothesize that predictions are not

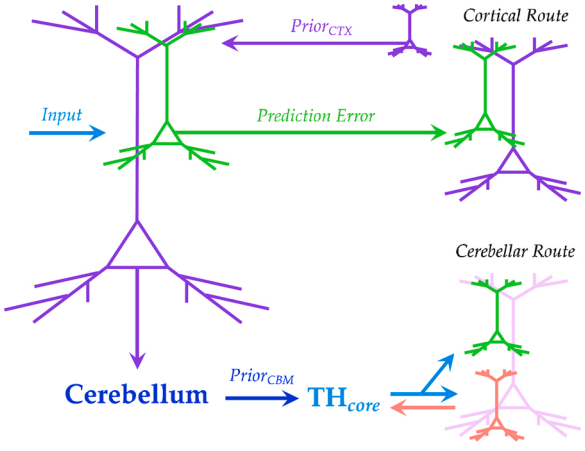

Fig. 4. Neural instantiations of predictive coding. In traditional models of predictive processing (Rao and Ballard, 1999), inputs enter a cortical region (light blue), where they are compared with predictions (or priors) from higher, more agranular regions of cortex ($Prior_{CTX}$; purple), likely from the descending axons of PT-type pyramidal cells. The differences between the Input and $Prior_{CTX}$ (i.e., Prediction Errors) are then fed back up the hierarchy by IT-type pyramidal cells (green), where they contact IT-type pyramidal cells, amongst other cells, in higher (i.e., more agranular) regions of cerebral cortex. In this Perspective, I suggest an alternative route for prior predictions to alter information flow in the cerebral cortex. Namely, efference copies from PT-type pyramidal cells that enter the cerebellum via the pontine nuclei (dark blue) can be used to provide a different form of prediction to distinct IT-type and CT-type pyramidal cells ($Prior_{CBM}$; dark blue), likely in different cortical regions than those that would have been contacted by locally-constrained IT-type cells.

solely conveyed through an agranular-to-granular flow of information within the cerebral cortex, but instead are also able to use a privileged short-cut that runs via the cerebellum (Fig. 4; $Prior_{CBM}$). Importantly, this capacity is inherent within the wiring of the central nervous system. Whenever a layer V PT-type pyramidal cell fires, it sends a corollary discharge signal to many areas in the sub-cortex (Harris and Shepherd, 2015; Solari and Stoner, 2011), including the pontine nuclei (Kratochwil et al., 2017; Tang and Nibley, 2019). In doing so, the activated cortical cell effectively recruits feedback from the cerebellar cortex (blue in Fig. 4), which has learned through supervised training (Montgomery and Perks, 2019) that is often conditioned on its own output (Khilkevich et al., 2018) to predict the precise sequence of patterns that will likely occur next within the particular context (Ebner and Pasalar, 2008; Jirenhed et al., 2017).

In a novel context, the core pathway is proposed to rapidly boost the best approximation of how to act in the particular context. This would have the effect of slightly raising the gain within a local cortical region (Dacre et al., 2019), which would in turn raise the likelihood of its involvement in the active coalition of regions that together define the current active state of the brain. Importantly, the prior mediated by cerebellar input would likely be more precise and rapid (Montgomery and Perks, 2019) than the relatively diffuse feedback from higher regions of the cerebral cortex regions (Friston and Price, 2001), which may instead represent a distribution of possible explanations for the precise constellation of activity within lower cortical areas. In this way, the cerebellum can be conceptualized as acting like a storage centre for the spatiotemporal patterns that have been learned over time to instantiate well-learned behaviour (Shine and Shine, 2014). These well-learned, context-specific responses can then be relied upon to complete whatever task the context defines, without requiring ongoing, on-line feedback from more deliberate, attentive processing modes in the cerebral cortex. In other words, the process can be 'delegated to automaticity' (Shine and Shine, 2014). Recent optogenetic, two-photon calcium recordings have confirmed that the cortex and cerebellum are strongly intertwined in precisely these contexts, and form a low-dimensional coalition as a function of learning towards automaticity (Wagner et al., 2019). The role of the thalamus in this model should also not be understated, as it likely provides crucial constraints over the dimensionality of the system (Shine et al., 2019a), both through its inherent circuitry (the thalamus contains a few orders of magnitude less neurons than the cortex), and through its capacity to provide constraints over precisely which cortical columns were able to remain active (Jones, 2001; Ward, 2011) and hence, form a part of each active neural coalition.

In humans, there has been a relatively late evolutionary expansion of the lateral frontal cerebral cortex (Ardesch et al., 2019; Krienen et al., 2016; Sereno et al., 2020), particularly in those regions subserving higher cognitive functions. Importantly, these regions did not expand on their own. Indeed, several components of the cerebellar circuitry, including the dentate nucleus (Baizer, 2014), pontine nuclei (Baizer, 2014), lateral cerebellar cortex (Ramnani, 2005), and the brainstem (Baizer, 2014) have also greatly expanded over recent phylogeny. The thalamic mediodorsal nucleus, which in humans receives inputs from ventrolateral dentate nuclei of the cerebellum, projects to the granular prefrontal cortices (Erickson and Lewis, 2004) and is strongly implicated in cognitive function (Rikhye et al., 2018; Shine et al., 2019b), also increased over recent evolutionary time (Mitchell and Chakraborty, 2013). Together, these results suggest that one of the crucial adaptations that facilitated our cognitive enhancement is our capacity to utilize the repetitive, automatic architecture of the cerebellar cortex to facilitate core system activity in the frontal cortex and hence, to support relatively automatic, anticipatory processes within the cognitive domain (Shine and Shine, 2014). Precisely how these relatively automatic processes impact upon traditional notions of cognitive function are a pivotal area for further study.

2.3. The neuronal basis of cognition and consciousness

The principal role of the thalamus in mediating whole-brain dynamics suggests that other higher-order emergent functions of the brain, such as cognition (Saalman and Kastner, 2015; Bell and Shine, 2019; Bolkan et al., 2017; Schmitt et al., 2017; Shine et al., 2019a, 2019b; Wolf and Vann, 2019), attention (Saalman et al., 2012) and awareness (Redinbaugh et al., 2020), rely prominently on the involvement of thalamic nuclei. In particular, the distributed architecture described above represents a plausible means for instantiating dual process theories of cognition (Kahneman, 2013; Shea and Frith, 2016). In these approaches, a distinction is typically made between fast, implicit, automatic processes (i.e., 'system one') and slow, deliberative, serial processes (i.e., 'system two') (Kahneman, 2013), although these two systems likely represent two points on a spectrum, rather than distinct categories in and of themselves. While these frameworks hold substantial explanatory power for cognitive function (Kahneman, 2013; Shea and Frith, 2016), their implementation in the brain has remained relatively poorly understood.

Based on the processes described above, I extend previous work (Balleine and Dickinson, 1998; Daw et al., 2011; Dayan, 2009; Graybiel, 2008; Robbins and Costa, 2017) by proposing that fast, parallel, associative functions of 'system one' are mediated by the sensory or cerebellar-driven core thalamic nuclei, which in turn shape feedforward activity via the granular layers of the cerebral cortex (Fig. 5A). Assuming sufficiently well-learned behaviours, this circuitry is well-suited to the support of relatively autonomous, parallel processing. In other words, adaptive, multi-regional patterns should be able to coordinate motoric or cognitive responses to ongoing challenges without forcing the system into a state dominated by the firing of one particular neural coalition. In contrast, I propose that the slow, deliberative processes of 'system two' are instead mediated by the matrix thalamic nuclei which, following disinhibition from the basal ganglia, non-linearly increase the gain of supra-granular regions of the cortex, and hence promote a more integrative, feedback-related mode of processing (Fig. 5B).

The action of system one and system two processes are also reminiscent of the 'multiple drafts' model of consciousness (Dennett, 1991), in which the activity distributed across a diverse array of autonomous, domain-specific sub-systems reflects subtle permutations of a particular brain state. The 'drafts' in this model refer to the numerous different possible interpretations of sensory input and background activity that are constantly processes by the relatively autonomous parallel processing system. In a manner reminiscent of the affordance competition hypothesis (Pezzulo and Cisek, 2016), this process supports the preparation of multiple actions in parallel, with the winning argument that emerges from a distributed consensus defining the active brain state (Cisek, 2012). Similar models have been proposed in an effort to explain the differing functions of the dopaminergic basal ganglia system (Keeler et al., 2014).

The winning draft that receives a boost sufficiently strong enough to cause a particular neural coalition to rise above the noisy background competition is proposed to define the contents of our conscious experience (Dennett, 1991; Fig. 5B). The victorious neural coalition is also awarded a protracted temporal influence relative to other regions in its local area. This means that the most active neural region will retain its activity over time relative to its neighbours and hence, enforce distinct, non-linear spatiotemporal constraints over the rest of the nervous system (Whyte and Smith, 2020), with the extent of the influence defined by the hierarchical level of the region (Honey et al., 2007). A draft is only promoted to consciousness if it is probed in a way that augments its activity – physiologically, this could occur either via inputs from the autonomously active structures of the ascending arousal system (yellow in Fig. 5B), matrix thalamic projections (range in Fig. 5B; Cruikshank et al., 2012) or through the more targeted feedback connections that project from agranular to granular cortices (purple in Fig. 5B). A key benefit of the multiple drafts model is that it does not rely on dualistic

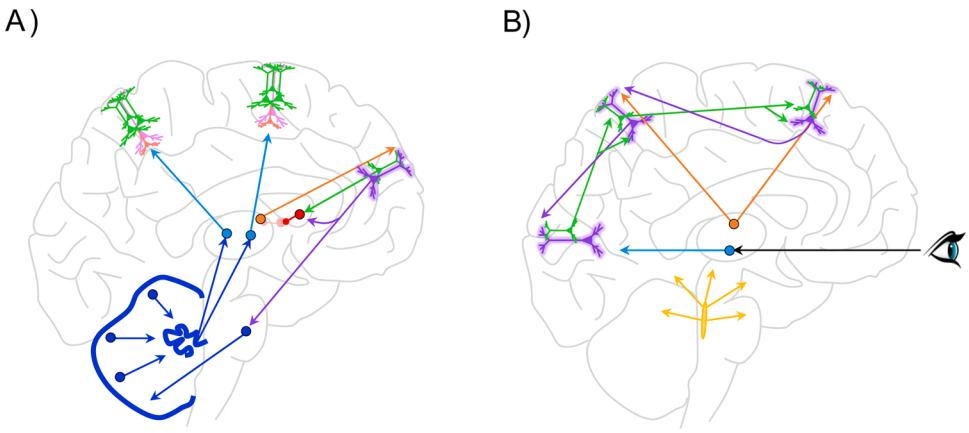

Fig. 5. Neural instantiations of dual-process models. A) System 1 processes are proposed to occur through cerebellar-mediated (dark blue) parallel processing, which is initially triggered by PT-type pyramidal cells (purple), which likely utilize striatal-mediated disinhibition of matrix thalamic nuclei (red and orange) to transition into burst-firing mode (purple glow) – note that the cerebellar support is such that the two neural coalitions that receive core matrix input (light blue) are able to function autonomously from one another (i.e., they can instantiate parallel processing); B) System 2 processes are proposed to occur when feed-forward (light blue; in this case via retinal activity) coincide with feed-back (purple) projections from PT-type pyramidal cells, causing an apical amplification and a transition into a burst firing mode. The likelihood of burst firing in PT-type pyramidal cells is augmented by both the matrix thalamic cells (orange) and the ascending arousal system (yellow), which both increase the gain of supragranular regions of the cerebral cortex. Key: arrow – excitatory; ball – inhibitory; faded colour – inhibited activity pattern.

philosophical arguments, however despite its clear utility, there is currently little clarity regarding the manner in which the model may be precisely instantiated in neural circuitry.

Like dual-process theories of cognition, the multiple drafts model of consciousness can be mapped onto the neurobiological processes detailed in this manuscript. The specific coalitions of PT-type pyramidal cells that are boosted by the intersection of cortical feedback and diffuse thalamic projections (along with the ascending arousal system; Phillips et al., 2016) offer a plausible mechanism for promoting primary conscious awareness. This mechanism thus shares similarities with both the mesocircuit model (Schiff, 2009) and the thalamic dynamic core model (Ward, 2011) of consciousness, which both imply that the formation of recurrent connections between the matrix thalamus and the supragranular regions of the cerebral cortex are a crucial substrate for promoting conscious awareness. Importantly, there is now empirical evidence from multiple optogenetic studies in rodents that demonstrates this very effect: augmenting arousal-sensitive thalamic and cortical projections to the apical dendrites of PT-type pyramidal cells affords a means for causally manipulating conscious state (Suzuki and Larkum, 2020; Takahashi et al., 2020). Thus, out of the background of relatively autonomous cortical regions firing in parallel, the simultaneous temporal coincidence of inputs to PT-type apical dendrites would shift the cell into a burst-firing mode (Larkum et al., 2009; Phillips et al., 2016), greatly impacting its capacity to influence other neural circuits, while also prolonging its temporal scale (Chan et al., 2016). This process would also impose seriality on the contents of conscious: any cortical region with PT-type pyramidal cells firing in burst mode would be incorporated into the conscious state (Aru et al., 2019), as if pulled into a dynamically evolving neural 'vortex' (Llinás, 2001). Crucially, seriality is a key characteristic of system two processing modes (Kahneman, 2013), and here emerges naturally from a biologically-motivated, distributed processing process that does not rely on the dualistic notion of a Cartesian Theatre.

Thalamocortical interactions have also been linked to attentional processes in the brain. Specifically, the connections between CT-type, layer VI pyramidal cells and the reticular nucleus, which is a thin sheet of inhibitory GABAergic neurons that wraps around the thalamus (Crabtree, 2018), have been hypothesized to imbue the brain with the capacity to blanket the activity within specific thalamic populations (Crick, 1984). Recently, empirical evidence for this hypothesis has been provided by optogenetic stimulation of the reticular nucleus in mice (Lewis et al., 2015). The implication is that cells that are not inhibited by the reticular nucleus will have relatively higher gain than their surrounding competitors, and hence, be able to better coordinate their activity with ongoing patterns in the cerebral cortex (Nakajima and Halassa, 2017; Fiebelkorn and Kastner, 2019). The pulvinar nucleus, which is comprised of both core and matrix populations (Münkle et al., 2000), is presumed to be particularly important for mediating attentional functions (Saalman and Kastner, 2015; Fiebelkorn et al., 2019), putatively by affording novel opportunities for cross-regional coordination (Saalman et al., 2012; Nakajima and Halassa, 2019) and temporal, working memory-related maintenance (Bolkan et al., 2017; Schmitt et al., 2017) in the cerebral cortex. Whether these effects are mediated by core or matrix thalamic cells remains an open question, though given their neuroanatomical capabilities, I predict that cells with predominantly matrix-like capacities will be crucial for these integrative functions (Clascà, et al., 2012).

3. Conclusion

To achieve distributed, complex, adaptive dynamics, the microscopic elements of the brain coordinate their activity into neural coalitions that ultimately facilitate cognition and behaviour. Evidence from diverse scientific fields suggests that the central nervous system might have solved this problem through elaborating distributed gradients of circuit complexity that integrate distinct compartments across the central nervous system. The thalamus in particular stands in focus as a crucial structure that lies at the intersection of the other major subcomponents of the central nervous system, allowing it to play an integrative role in systems-level dynamics (Hwang et al., 2017). I have argued that the mesoscopic interactions between the thalamus and the rest of the brain imply that the diencephalic structure is well-placed to shape the coordinated dynamic interactions between the cerebral cortex, basal ganglia, cerebellum and tectum (amongst others) that give rise to our abilities to attend, think and experience the world around us. In this ochlocratic scenario, ensuring low-dimensional, normalizing constraint over the distributed dynamics of the central neural system are of paramount importance. The thalamus is ideally placed to instantiate this control. In other words, the distributed, complex system under the constraint of the thalamus is a working process model for effective brain function.

A number of caveats to this perspective of whole brain function are worth mentioning. Firstly, the organizing principle described in this

manuscript is but one vantage point through which to view the complex, multi-scale, heterarchical (i.e., integrated yet decentralized; McCulloch, 1945) structure of the central nervous system. Other approaches that utilize different anatomical (Gerfen, 1989; Halassa and Sherman, 2019) or functional (Fries, 2015; Varela et al., 2001) signatures to understand the organization of the brain will likely provide unique insights to those identified here. Secondly, measuring a distributed, multi-scale system is inherently challenging, particularly given that we don't yet know the precise relationship between cell-class specific activity and commonly used summary measures available through whole brain neuroimaging (Logothetis et al., 2001). Until these relationships are better defined, testing the predictions of the model will remain challenging.

Thirdly, I explicitly chose not to focus the descriptions in this manuscript on either mnemonic (Aggleton et al., 2010; Wolff and Vann, 2019) or emotional (Pessoa, 2017; 2019) processes, both of which have been shown to crucially relate to thalamic involvement. There are also important implications for thalamic damage in clinical disorders (e.g., Power and Looi, 2015; Pergola et al., 2018) that are similarly out of the scope of this manuscript. I expect that future work in the field will help to incorporate these concepts into the dynamical systems framework. In addition, computational modelling approaches that embrace the heterogeneity inherent within neurobiology (e.g., Bonjean et al., 2012; Demeritas et al., 2019; Müller et al., 2020b) will undoubtedly provide important insights for how the neuroanatomical details presented here impact systems-level dynamics. Finally, many of the neurobiological details in this manuscript will undoubtedly be refined with the advent of more detailed measurement techniques. However, from a dynamical systems standpoint, the processes described in this manuscript are considered to be more important for the systems' function than their precise implementation.

In conclusion, I have argued that a dynamical systems perspective is a crucial lens through which to view higher brain function, and that the thalamus is ideally placed to shape and constrain the dynamic patterns that emerge from coordinated interactions within this architecture.

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Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with this article can be found in the online version: https://doi.org/10.1016/j.pneurobio.2020.101787.

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